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Docket No.: 5986/17686-USA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: John W. BARNWELL

Serial No.: 09/667,130

Art Unit: 1645

Filed: September 21, 2000

Examiner: P. Duffy

For: **PLASMODIUM VIVAX BLOOD STAGE ANTIGENS,  
ANTIBODIES AND DIAGNOSTIC ASSAYS**

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October 17, 2000

Honorable Commissioner of Patents  
and Trademarks  
Washington, DC 20231

DECLARATION OF DONALD CROTHERS

I, Donald Crothers, declare and state as follows:

BACKGROUND

1. I, Dr. Donald Crothers, am currently the Sterling Professor of Chemistry and Professor of Molecular Biophysics and Biochemistry at Yale University in New Haven, Connecticut, and have been at the post since 1997. I was Chairman of the Chemistry Department at Yale University from 1993 to 1999. In addition, I was the Alfred E. Kemp

Concluded  
6/28/02  
DRD

Professor of Chemistry at Yale University from 1985 through 1996, and I have been an Assistant Professor, Associate Professor, and Professor at Yale University since 1964. Throughout my over 36 year career at Yale University, I have published numerous articles and have taught many courses in the area of Biochemistry and Molecular Biology, as can be seen in my attached *curriculum vitae*. In particular, my research has focused on nucleic acids, which I have been informed is the subject matter of the present patent application.

2. I have been a member of various advisory and editorial boards for journals in the area of Biochemistry, Biophysics, and Molecular Biology, including the Journal of Molecular Biology (1971-1975); Nucleic Acids Research (1973-1982); and Biochemistry (197-1979). I have also served on committees such as the Visiting Committee for the Brookhaven National Laboratory Biology Department (1992-1997).

3. I am not a co-inventor of the present application, and I do not have a financial interest in the present application, nor in the outcome of the present proceedings. I also do not have a financial interest in New York University or in the Beckton Dickinson Corporation, which I have been informed have certain rights in this invention.

4. In preparation for my Declaration, I have reviewed in detail the specification for the present application, and *Southern, Journal of Molecular Biology*, 98:503 (November 1975) (hereinafter the "Southern publication").

5. My understanding of the invention as described in the specification is that the invention relates to isolated, purified polynucleotides encoding for a *Plasmodium vivax* protein or fragments thereof. It is my understanding that these proteins or protein fragments are to be used for the preparation of diagnostic assays for the detection and selective identification of *Plasmodium vivax* in liquid biological samples.

### **QUESTION CONSIDERED**

6. In connection with my retention as an expert in the present application, I have been asked to consider the following question which I understand is relevant to the issue of patentability of the claims in the present application. The question is as follows:

(i) Whether as of June 2, 1993, a person of ordinary skill in the foregoing field would have recognized the hybridization conditions as disclosed in the Southern publication as stringent conditions.

### **CONCLUSION**

7. I have reviewed the above question, and based on the materials provided to me, as well as my experience as a researcher, author, lecturer and peer review editor in the field of biochemistry, and in particular in the area of nucleic acids, I conclude that a person of ordinary skill in the art, at the relevant time, would have recognized that all of the hybridization conditions as set forth in the Southern publication are stringent hybridization conditions and that any set of the disclosed conditions would have resulted in selection of a hybrid between a nucleic acid of interest to an investigator and its complement.

8. My conclusion is based on examination of the experimental conditions explored and used in the Southern publication. Stringent hybridization is typically carried out at the temperature that maximizes the hybridization rate of the target duplex (and therefore minimizes improper hybrid formation). It is generally found that this temperature occurs about 20 degrees Celsius below the melting temperature of the hybrid duplex, typically 65°C in the SSC buffer

commonly used at that time. Southern used 65°C for hybridization in SSC, and showed that the rate was a maximum at 80°C in 6X SSC, as shown in Figure 5 of the Southern publication. As shown in Figure 6, 80°C was then chosen as the appropriate temperature for hybridization in 6X SSC, i.e. the temperature at which improper hybrid formation would be minimized at the higher salt concentration of 6X SSC. Both sets of conditions 65°C/1X SSC and 80°C/6X SSC are stringent conditions, and they would have been readily recognized as such by a person of ordinary skill in this field well prior to 1993. The conditions of 65°C and 2X SSC are also stringent. Southern states that the results under these conditions were the same as at 80°C and 6X SSC

A second important feature of stringent conditions is a wash period at the hybridization temperature. This process selectively removes the improper hybrids because they have a more rapid dissociation rate than the target duplex. This protocol was used by Southern, as described on page 508 of the Southern publication.

The fact that the Southern publication does not refer to these hybridization conditions as stringent conditions is not an indication of lack of stringency. Although the term was known in 1972 at the time of the Southern publication, it was not in common use until after 1975. Nevertheless, the concept of stringency (i.e., the concept that the intrinsic specificity of the hybridization reactions depends on the annealing conditions employed), was familiar to those of ordinary skill in the field. I am confident that, in 1993, a person of ordinary skill in the field would have recognized the hybridization conditions as disclosed in the Southern publication as what we would now call (and did call in 1993) stringent conditions.

9. Finally, I declare that all statements that I have made herein of my own knowledge are true, and that all statements that I have made herein on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

10/17/2002

Date

Donald M. Crothers

Donald Crothers

## BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.



NAME	POSITION TITLE
Donald M. Crothers	Sterling Professor of Chemistry Professor of Molecular Biophysics & Biochemistry

**EDUCATION** (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Yale University, New Haven, CT	B.S.	1958	Chemistry
Cambridge University, Cambridge, U.K.	B.A.	1960	Biochemistry
U. California, San Diego, CA	Ph.D.	1963	Chemistry
Max-Planck-Institute, Göttingen, Germany	Postdoc	1964	Biophysics

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE:** Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

**Professional Experience:**

*Yale University, Departments of Chemistry and Molecular Biophysics and Biochemistry*

Assistant Professor	1964-1968
Associate Professor	1968-1971
Professor	1971-
Alfred E. Kemp Professor	1985-1996
Sterling Professor	1997-
Chairman of Chemistry	1975-1981; 1993-present

**Ancillary Professional Positions:**

Editorial Board, Journal of Molecular Biology	1971-1975
Editorial Board, Nucleic Acids Research	1973-1982
Advisory Board, Biopolymers	1973-
Editorial Board, Biochemistry	1975-1979
Biophysics Biophysical Chemistry B Study Section (NIH) (Chairman 1974-1976)	1972-1976
Co-Chairman, Nucleic Acids Gordon Conference	1975
Council Member, Biophysical Society	1979-1982
Publications Committee, Biophysical Society	1982-1985
Editorial Board, Ann. Rev. Phys. Chem.	1981-1985
Biophysics Review Committee, Swedish National Research Council	1982
Visiting Committee, Brookhaven National Laboratory Biology Dept.	1992-1997

**Honors:**

National Finalist, Westinghouse Science Talent Search	1954
Yale B.S. Summa cum Laude, with exceptional distinction in Chemistry 1958	
Mellon Fellow at Clare College, Cambridge	1958-1960
Cambridge B.A. - Class I Honours	1960
NSF Postdoctoral Fellow	1963-1964
Sloan Foundation Fellow	1966
Yale Science and Engineering Award for Contributions to Basic and Applied Science	1977
Guggenheim Fellow	1978-1979
Alexander von Humbolt U.S. Senior Scientist Award	1981
Fellow, American Academy of Arts and Sciences	1986
Member, National Academy of Sciences	1987

Fellow, American Association for the Advancement of Science

1992

Recent Publications:

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240. The Position of Site-Directed Cleavage of RNA using RNase H and 2'-O-methyl Oligonucleotides is Dependent on the Enzyme Source, J. Lapham, Y.-T. Yu, M.-D. Shu, J. A. Steitz, and D. M. Crothers, *RNA* **3**, 950-951 (1997).
241. Measurement of Diffusion Constants for Nucleic Acids by NMR, J. Lapham, J. P. Rife, P. B. Moore, and D. M. Crothers, *J. Biomol. NMR* **10**, 255-262 (1997).
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Donald M. Crothers

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